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| 10/674,414 | 10/01/2003 | Minoru Ueda | TEI-0128 | 5142 |

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| EXAMINER | |
|---|---|
| FORD, ALLISON M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1651 | |

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/674,414 | UEDA ET AL. | |
| | Examiner | Art Unit | |
| | Allison M Ford | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) 7-9 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6, 10-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-12 are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-6 and 10-12, drawn to method for producing artificial cartilage, classified in class 435, subclass 377.

II. Claims 7-9, drawn to an apparatus for manufacturing artificial cartilage, classified in class 435, subclass 285.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP § 806.05(e)). In this case the ultrasound apparatus of Invention II can be used to promote transfection of nucleic acids into cellular material, such as grafts, prior to transplantation; wherein the nucleic acids would promote resistance to common tissue-specific cellular defects.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classifications, the search required for each of the groups are not required for the other groups, and because of the divergent subject matter restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Dutton on 7/29/2004 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-6 and 10-12. Affirmation of this election must be made by applicant in replying to this Office action. Claims 7-9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a method of manufacturing artificial cartilage, characterized in that undifferentiated mesenchymal cells are cultured in a cartilage differentiation inducing medium, and the cells are irradiated with ultrasound. Claim 2 requires the ultrasound to have a frequency of 20 kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 Hz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 3 requires the ultrasound to have a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 4 is drawn to artificial cartilage produced by ultrasound irradiation of undifferentiated mesenchymal cells under cultivation in a cartilage differentiating inducing medium. Claim 5 requires the ultrasound to have a frequency of 20 kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 Hz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 6 requires the ultrasound to have a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$.

It is unclear what applicant is regarding as "artificial cartilage." Artificial cartilage includes chondrocyte cells, numerous proteins, and extracellular matrix (See Roughly, pg 342). It is unclear if applicant is intending to claim a culture of chondrocytes as artificial cartilage, or if the method produces complete, functional cartilage. It is unclear what applicant is trying to claim as "artificial cartilage" and thus the claims are rendered indefinite.

It is further unclear and confusing what applicant is regarding as "cartilage differentiation inducing medium." Cartilage does not differentiate. The specifications refer to a "cartilage-

forming and differentiation inducing basal medium" it is unclear if this is the same medium (See spec pg 7). It is further unclear if they are referring to a medium that induces the entire process of differentiating, or just induces the initiation of differentiation. It is still further unclear if Applicant is referring to the differentiation of cartilage cells, the differentiation of undifferentiated mesenchymal cells into chondrocytes, the maturation of chondrocytes into artificial cartilage tissue, or the entire process from undifferentiated mesenchymal cells to chondrocytes to artificial cartilage.

Additionally it is not defined at what point the ultrasound is applied, and to what cells. It indiscernible if the ultrasound is applied to the undifferentiated cells, differentiated chondrocytes, or fully formed cartilage. Therefore the claims are unclear and confusing, and thus indefinite.

Claims 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 10 is directed to a method of accelerating cartilage differentiation induction by irradiating undifferentiated mesenchymal cells with ultrasound. Claim 11 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 12 requires the ultrasound to have a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0kHz, and an ultrasound intensity of 5-120 $mW/cm^2$.

It is unclear what Applicant intends by the phrase "cartilage differentiation induction." It is unclear if they are referring to accelerating the entire process of differentiating, or just accelerating the initiation of differentiation. Further, it is unclear if Applicant is referring to the differentiation of cartilage cells, the differentiation of undifferentiated mesenchymal cells into chondrocytes, the maturation of chondrocytes into artificial cartilage tissue, or the entire process from undifferentiated mesenchymal cells to chondrocytes to artificial cartilage.

Additionally it is not defined at what point the ultrasound is applied, and to what cells. It indiscernible if the ultrasound is applied to the undifferentiated cells, differentiated chondrocytes, or fully formed cartilage. The language is unclear and confusing with respect to the claim language, and thus the claims are deemed indefinite.

Please note that the language of a claim must make it clear what subject matter the claim encompasses to adequately delineate its "metes and bounds." See, e.g., the following decisions: In re Hammack, 427 F 2d. 1378, 1382, 166 USPQ 204, 208 (CCPA 1970); In re Venezia 530 F 2d. 956, 958, 189 USPQ 149, 151 (CCPA 1976); In re Goffe, 526 F 2d. 1393, 1397, 188 USPQ 131, 135 (CCPA 1975); In re Watson, 517 F 2d. 465, 477, 186 USPQ 11, 20 (CCPA 1975); In re Knowlton 481 F 2d. 1357, 1366, 178 USPQ 486, 492 (CCPA 1973). The courts have also indicated that before claimed subject matter can properly be compared tot he prior art, it is essential to know what the claims do in fact cover. See, e.g., the following decisions: In re Steele, 305 F 2d. 859, 134 USPQ 292 (CCPA 1962); In re Moore 439 F 2d. 1232, 169 USPQ 236 (CCPA 1969); In re Merat, 519 F 2d. 1390, 186 USPQ 471 (CCPA 1975).

***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kandel (US Patent 5,326,357), Parvizi et al, Nishikori et al, and Pittenger (WO 98/32333-A1).

Applicant's claim 4 is directed to artificial cartilage that has been produced from undifferentiated mesenchymal cells cultured in cartilage differentiation inducing medium, and exposed to ultrasound irradiation. Claim 5 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 6 requires the ultrasound to have a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0kHz, and an ultrasound intensity of 5-120 $mW/cm^2$.

The product as claimed is determined to be a product-by-process claim. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

- Kandel teaches artificial cartilage (See col. 3, ln 35-36).

- Parvizi et al teach artificial cartilage (See pg 489, col. 2).

- Nishikori et al teach artificial cartilage (See pg 203, col. 2).

- Pittenger et al teach artificial cartilage (See pg 20).

Therefore, the references anticipate the claimed subject matter.

***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kandel (US Patent 5,326,357), Parvizi et al, Nishikori et al, and Pittenger (WO 98/32333-A1).

Applicant's claim 4 is directed to artificial cartilage that has been produced from undifferentiated mesenchymal cells cultured in cartilage differentiation inducing medium, and exposed to ultrasound irradiation. Claim 5 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 6 requires the ultrasound to have a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0kHz, and an ultrasound intensity of 5-120 $mW/cm^2$.

The product as claimed is determined to be a product-by-process claim. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

- Kandel teaches artificial cartilage (See col. 3, ln 35-36).

- Parvizi et al teach artificial cartilage (See pg 489, col. 2).

- Nishikori et al teach artificial cartilage (See pg 203, col. 2).

- Pittenger et al teach artificial cartilage (See pg 20).

Therefore, the references anticipate the claimed subject matter.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pittenger et al (WO 98/32333-A1) in view of Parvizi et al.

Applicant's claim 1 is directed to a method of manufacturing artificial cartilage; comprising culturing undifferentiated mesenchymal cells in a cartilage differentiation inducing medium, and irradiating cells with ultrasound. Claim 2 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Applicant demonstrates the manufacturing of cartilage by increasing production of aggrecan protein (See spec. pg 9). Claim 10 is directed to a method of accelerating cartilage differentiation induction by irradiating undifferentiated mesenchymal cells with ultrasound. Claim 11 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Applicant demonstrates the acceleration of cartilage differentiation induction by increasing production of aggrecan proteins (See spec, pg 9).

Pittenger et al teaches manufacturing artificial cartilage, comprising culturing undifferentiated mesenchymal stem cells in a chondroinductive medium that contains TGF-β3 (See pg 16). Pittenger et al teach the undifferentiated cells developing into a culture of chondrocyte cells (See pg 4).

Pittenger et al do not teach irradiating cells with ultrasound.

Parvizi et al teach irradiating cultures of chondrocyte cells with ultrasound to increase aggrecan mRNA and protein by the chondrocytes, which applicant is calling artificial cartilage (Claims 1 and 10) (See pg 491, col. 2). Parvizi et al also teaches using an ultrasound treatment having a frequency of 1.0 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an ultrasound intensity of 50 and 120 $mW/cm^2$ (two separate treatment groups) (Claims 2 and 11) (See pg 489, col. 2). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to irradiate the culture of chondrocytes with ultrasound. The person of ordinary skill in the art would have been motivated to develop cultures of chondrocytes and then irradiate the culture of with ultrasound in order to upregulate gene and protein expression (See pg 492, col. 2) to promote tissue generation. One would expect success because use of ultrasound to stimulate biological responses such as gene and protein expression is a common practice in the art (See for example, Parvizi et al). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-3, and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pittenger et al (WO 98/32333-A1) in view of Nishikori et al.

Applicant's claim 1 is directed to a method of manufacturing artificial cartilage; comprising culturing undifferentiated mesenchymal cells in a cartilage differentiation inducing medium, and irradiating cells with ultrasound. Claim 2 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 3 requires the ultrasound to have a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Applicant demonstrates the manufacturing of cartilage by increasing production of aggrecan protein (See spec. pg 9). Claim 10 is directed to a method of accelerating cartilage differentiation induction by irradiating undifferentiated mesenchymal cells with ultrasound. Claim 11 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Claim 12 requires ultrasound to have a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Applicant demonstrates the acceleration of cartilage differentiation induction by increasing production of aggrecan proteins (See spec, pg 9).

Pittenger et al teaches manufacturing artificial cartilage, comprising culturing undifferentiated mesenchymal stem cells in a chondroinductive medium that contains TGF-β3 (See pg 16). Pittenger et al teach the undifferentiated cells developing into a culture of chondrocyte cells (See pg 4).

Pittenger et al do not teach irradiating cells with ultrasound.

Nishikori et al teach irradiating cultures of chondrocyte cells with ultrasound to increase aggrecan expression by the chondrocytes, which applicant is calling artificial cartilage (Claims 1 and 10) (See pg 202, col. 1). Nishikori et al also teaches using an ultrasound treatment having a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an ultrasound intensity of 30 $mW/cm^2$ to promote proliferation (See pg 202, col. 2) (Claims 2, 3, 11, and 12). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to develop cultures of chondrocytes and then irradiate the culture with ultrasound. The person of ordinary skill in the art would have been motivated to irradiate the culture of chondrocytes with ultrasound in order to increase aggrecan production by chondrocytes in articular cartilage for tissue generation. One would expect success because use of ultrasound to stimulate a biological response by influencing cell activity, such as increasing gene and protein expression, is a common practice in the art (See for example, Nishikori et al). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pittenger in view of Wu et al.

Applicant's claim 10 is directed to a method of accelerating cartilage differentiation induction by irradiating undifferentiated mesenchymal cells with ultrasound. Claim 11 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 $mW/cm^2$. Applicant

demonstrates the acceleration of cartilage differentiation induction by increasing production of aggrecan proteins (See spec, pg 9).

Pittenger et al teach differentiating undifferentiated mesenchymal cells into artificial cartilage, comprising culturing undifferentiated mesenchymal stem cells in a chondroinductive medium that contains TGF-β3 (See pg 16). Pittenger et al teach the undifferentiated cells developing into a culture of chondrocyte cells (See pg 4).

Pittenger et al do not teach irradiating cells with ultrasound.

Wu et al teach applying ultrasound treatment to chondrocyte cultures to promote expression of aggrecan mRNA, which applicant is calling artificial cartilage (See col. 1). Wu et al further teach applying ultrasound having a frequency of 1.0 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an intensity of 50 and 120 $mW/cm^2$ (separate trials) (Claim 11).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to accelerate cartilage differentiation induction by irradiating undifferentiated mesenchymal cells with ultrasound. One would have been motivated to optimize the parameters of the ultrasound as a matter of routine experimentation and optimization. One would expect success because use of ultrasound to stimulate a biological response, such as increasing gene expression, is a common practice in the art (See for example, Wu et al). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0927. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

AMF